原　著

INFLUENCE OF PROLONGED ANOXIA UPON THE BRAIN OF THE FETAL AND ADULT RABBIT

by

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Since the time of Little (1862) it has been believed that abnormal parturition, difficult labour, premature birth, and asphyxia neonatorum play important roles in the development of cerebral palsy. Autopsy of fetuses and newborns revealed, in a large number of cases, violent intracranial hemorrhages from rupture of the cerebral veins, especially the great cerebral vein of Galen and the superior cerebral veins. From these findings, it has generally been recognized that hemorrhage from rupture of the superior cerebral veins is located toward the vertex of the brain, thus affecting chiefly the legs, or the hemorrhage may extend lower on the cortex and also affect the arms, resulting not infrequently in a high decorticate state, in which the reflexes of Magnus and de Kleyn and the righting reflexes are developed. Furthermore, it is supposed that typical decerebration or localized destruction of the striate nuclei and the thalamus may be caused by hemorrhages from rupture of the internal veins or the great cerebral vein of Galen through which the blood from the interior of the brain drains.

Yagi (1935) classified the causation of asphyxia of newborn into three groups:

(1) The first group: General congestion in the fetal body (due to the umbilical or placental hindrances) → disturbance of the fetal heart → disturbance of gas exchanges → excitement or paralysis of the respiratory center → premature respiration → asphyxia (asphyxia suffocatoria s. pulmonalis)

(2) The second group: Cranial stress (natural or artifical) → elevation of intracranial pressure → cerebral lesion or intracranial hemorrhage → asphyxia (asphyxia apoplectica s. cerebralis)

(3) The third group: Anomalies of the heart → weakness of the heart beat → asphyxia (asphyxia cardialis)

Yagi reported that intracranial hemorrhage with or without laceration of the dura mater was found in 135 of 357 cases of neonatal death. He emphasized that in the mechanism of the hemorrhage three cranial factors— stasis, stress and resistance —play important roles, acting supplementally to one another.

The American Academy of Cerebral Palsy (1955) presumed that anoxia, cerebral

hemorrhage and contusions are the causative natal factors responsible for approximately 30 per cent of all cases. WINDLE and BECKER (1953) examined the effect of acute anoxia for a duration of about 8 minutes on the brain of the fetal guinea pig. In this experiment, multiple capillary hemorrhages and occasionally larger ones were found in all animals between 3 hours and 5 days after resuscitation, in half between 30 minutes and 2 hours, and in none killed by the asphyxia. Futhermore, cytologic changes were found in all specimens between one and one-half hours and 21 days after resuscitation. These pathological changes in the fetal guinea pig brain caused by acute anoxia of short duration bear some resemblance to those in the human fetal brain. However, hemorrhage large enough to cause death of the newborn never occourred in their experiment. Human fetuses are occasionally subjected to prolonged anoxial conditions during birth. It should be of great interest to study the effect of prolonged anoxia on the fetal brain.

Material and Method

Twenty non-pregnant adult rabbits and five pregnant rabbits close to term, 25 to 28 days after fertilization, were used for the experiment. In the present investigation, in order to study the effectiveness of prolonged anoxia on the brain, it was decided to utilize the simple expedient of placing the animal in a closed container, in which the rabbit consumed the oxygen, finally being asphyxiated. Only air was in the container at the start. With the consumption of the oxygen, the animal underwent a period of excitement, finally falling into convulsions one and one-half to three hours after the beginning of the experiment. It was then removed and resusciated by artificial respiration. This procedure was carried out once in four pregnant animals, and twice at an interval of 24 hours in another one. One animal died from asphyxia, and three were killed 6 to 24 hours after resuscitation. The fetuses were removed by Cesarean section. The remaining one was delivered by normal labor on the day following the experimental procedure. The fetal brain was exposed by partial resection of the skull, observed macroscopically, and removed from the skull after fixation in ethyl alcohol. In the non-pregnant adult rabbit, the experimental procedure mentioned above was carried out repeatedly at an interval of two to three days. Sections from fetal and adult brains were cut and stained with hematoxylin-eosin and by the method for showing Nissle bodies. Moreover, sections from adult brains were stained by methods for the demonstration of the neuroaxon, myelin sheath and lipoid.

Results

1. Influence of Anoxia upon the Brain of the Fetal Rabbit

The results of the present experiments are briefly shown in Tables 1 and 2. In these experiments, 20 dead fetuses and 23 newborns were obtained. Of the dead fetuses, 14 were mature and 6 were immature.

In all dead mature fetuses, violent and extensive hemorrhages from rupture of superior cerebral veins, the sagittal sinus, the great cerebral vein of Galen and the

Table. 1

case No.		1	2	3	4	5	Total	Control		
Number of times of experimental procedure performed		1	1	1	2	1				
Type of delivery		Cesarean section				Normal delivery				
Time lapsed from anoxia to removal of fetus (hrs.)		2	12	24	6	12				
Number and condition of fetuses and newborns removed	alive	7	1	3	6	6	23	10	6	6
	dead	0	10	1	3	0	14	0	0	0
	immature and dead	3	0	2	1	0	6	1	0	1
Total		10	11	6	10	6	43	11	6	7

Table. 2 Macroscopic Findings in the Brain of Fetuses and Nowborns

Case No.	Type of delivery	Macroscopic finding of the brain			Total
		Normal	Stasis	Hemorrhage from rupture of the cerebral veins	
1	Cesarean section	2	3	2	7
2		0	0	1	1
3		0	1	2	3
4		1	1	4	6
5	Normal delivery	2	2	2	6
Total		5	7	11	23

cerebellar veins were observed (Figs. 1, 2 and 3). The brains were totally necrosed and softened.

In 12 cases of newborns, no hemorrhage was macroscopically seen. In remaining 11 cases, moderate hemorrhages from rupture of the sagittal sinus, the superior cerebral veins and the cerebral vein of Galen were found. In addition, in the majority of the latter cases, mild hemorrhages from rupture of the cerebellar veins and the basal veins and frequently hemorrhage into the tela chorioidea were also seen (Figs. 4, 5 and 6). However, neither extensive hemorrhage nor capillary leakage in the grey and white matter was observed in any of these cases. In most cases involving newborns with or without intracranial hemorrhage, no pathological change in the nerve cells was detected. But, in three cases with intracranial hemorrhage, extensive or localized areas of necrosis were found. These pathological changes in the brain were briefly summarized in Table 3. The findings in individual cases will be described.

Case 4-1. In this case, the pregnant rabbit was subjected to anoxia two times at an interval of 24 hours. The newborn was removed by Cesarean section 6 hours after the end of the experiment. Macroscopically, explosive hemorrhages from rupture of the superior cerebral veins, the great cerebral vein of Galen and the cerebellar veins were observed (Figs. 7 and 8). The cerebrum and the brain stem were totally necrosed (Fig. 9). This pathological change is equivalent to low decerebration.

Case 5-1. The newborn was born 12 hours after resuscitation. In this case,

Table. 3 Hemorrhage from Rupture of the Cerebral Veins and Changes in Nerve Cells

Pathological changes \ case No.		4-1	5-1	5-2
Hemorrhage from rupture of the cerebral veins	S. sagittalis	###	−	−
	Vv. cerebri sup.	###	##	+
	V. cerebri magna (Galeni)	##	+	###
	V. chorioidea	+	−	+
	Vv. cerebelli sup.	###	##	+
	V. basalis	+	+	##
Change in the nerve cells	Cerebral cortex	total necrosis	necrosis of both parietal lobes	necrosis of both frontal lobes
	Basal ganglia	total necrosis	—	—
	Brain stem	total necrosis	—	—
	Cerebellum	—	—	—

marked hemorrhages from rupture of the superior cerebral veins and moderate hemorrhages from rupture of the great cerebral vein of Galen and the cerebellar veins were observed (Fig. 10). Histological examination revealed total necrosis of both frontal lobes, whereas the other parts of the brain remained intact (Figs. 11 and 12). This pathological change is equivalent to high decerebration.

Case 5-2. The newborn was born 12 hours after resuscitation. In this case, violent hemorrhage from rupture of the great cerebral vein of Galen and mild hemorrhages from rupture of the superior cerebral veins and the superior cerebellar veins were visible to the unaided eye (Figs. 13, 14 and 15). Histological examination revealed localized necrosis of both parietal lobes, while the other parts of the brain remained intact (Figs. 16 and 17).

2. Influence of Anoxia upon the Brain of the Adult Rabbit

In all twenty cases, neither hemorrhage nor marked congestion in the brain was macroscopically observed. However, in the animal subjected to anoxia repeatedly more than five times, histological examination proved a widespread absence of myelin and slight degenerative change in the nerve cells. The white matter throughout the brain and spinal cord was replaced by cystic tissue, in which no myelin could be found. The cysts varied in size from approximately 20 to 100 microns (Figs. 18 and 19). There was no marked increase in the number of glial cells. In the spongy area, no glial cells were found. The special stains used failed to show myelin break-down products. No sudanophilic droplets were seen. In most areas of spongy degeneration, no axon was stained (Fig. 20). The spongy tissue did not encroach on the grey matter. Although the majority of the nerve cells were well preserved throughout the brain, a small number of the nerve cells with slight degenerative changes such as cytolysis and shrinkage were scattered in the grey matter. This pathological change increased in extent and intensity with the number of times that the experimental procedure was performed.

Discussion

As described above, autopsy of the human newborn suggests that violent

intracranial hemorrhages play a most important role in causing cerebral palsy of Little's type. Moreover, it has long been supposed that anoxia during birth is the main cause for intracranial hemorrhage in the newborn. In addition, in the human newborn removed by Cesarean section, typical intracranial hemorrhage was not so infrequently found. In the present experiment, prolonged anoxia gradually progressing in intensity caused massive intracranial hemorrhages from rupture of the superior cerebral veins and the great cerebral vein of Galen, resulting in extensive or localized necrosis of the brain. These pathological changes bear a great similarity to those in the human newborn caused by birth injuries. From these pathological and clinical facts, it is thought that prolonged anoxia of the fetus during birth plays a most important role in causing intracranial hemorrhage, which may become expansive through trauma occurring during labor.

In contrast, the brain of the adult rabbit shows strong resistance to anoxia. However, in present experiment, the prolonged anoxia repeatedly performed caused, without exception, spongy change in the white matter throughout the brain and spinal cord. WOLMAN (1958) reported a case of a male child aged 16 months with quadriplegia due to spongy degeneration of the brain, which was similar to that observed in the present experiment.

Summary

(1) The influence of prolonged anoxia upon the brain of fetal and adult rabbits was studied.

(2) The pregnant rabbit close to term was placed in a container, in which the animal consumed the oxygen in the air, finally being asphyxiated one and one-half to three hours after the beginning of the experiment.

(3) In this experiment, 14 dead mature fetuses and 23 newborns were obtained. In all cases of dead fetuses, violent hemorrhages from rupture of the superior cerebral veins, the sagittal sinus, the great cerebral vein of Galen and the cerebellar veins occurred, resulting in total necrosis of the brain. In 11 cases of newborns, moderate hemorrhages from rupture of the cerebral veins were seen. In 3 of these instances, extensive or localized areas of necrosis of the brain were found. These cerebral changes in rabbit were similar to those in the brain of the human newborn produced by birth injuries.

(4) In the adult rabbit, prolonged anoxia repeatedly performed produced spongy degeneration in the white matter throughout the brain and spinal cord.

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Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

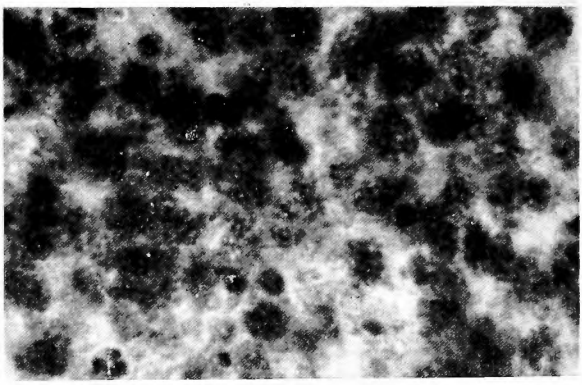

Fig. 9

Fig. 10

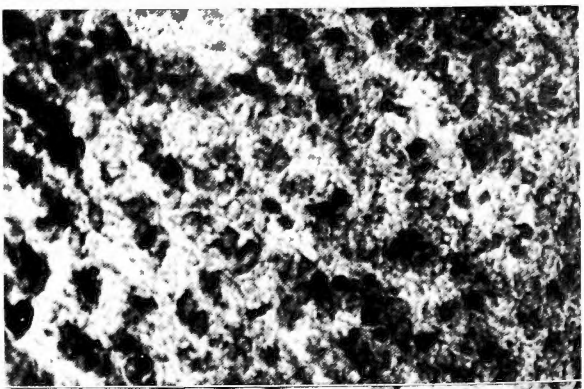

Fig. 11

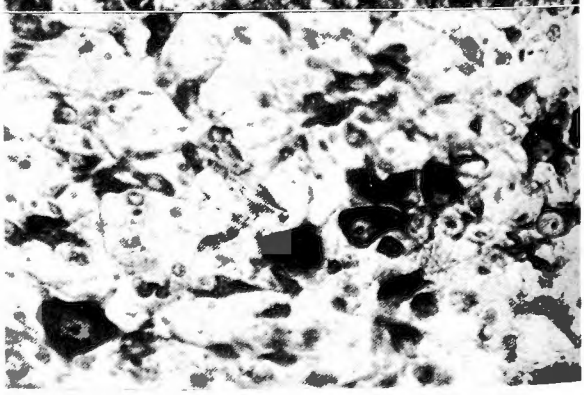

Fig. 12

Fig. 13

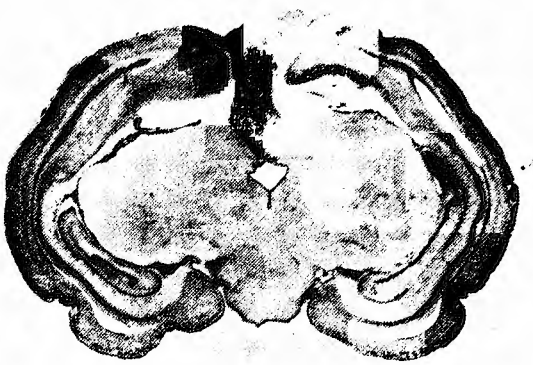

Fig. 14

Fig. 15

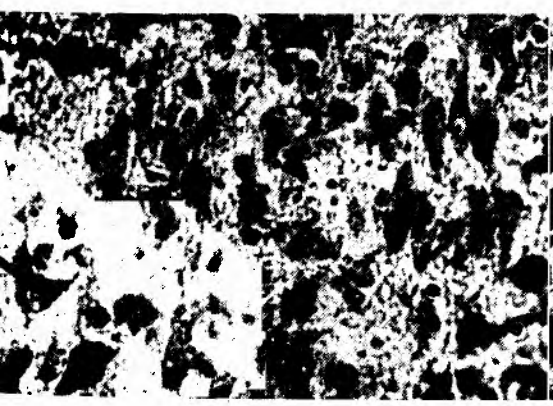

Fig. 16

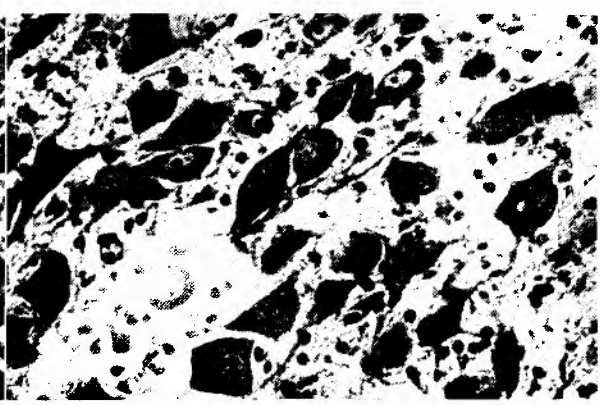

Fig. 17

Fig. 18

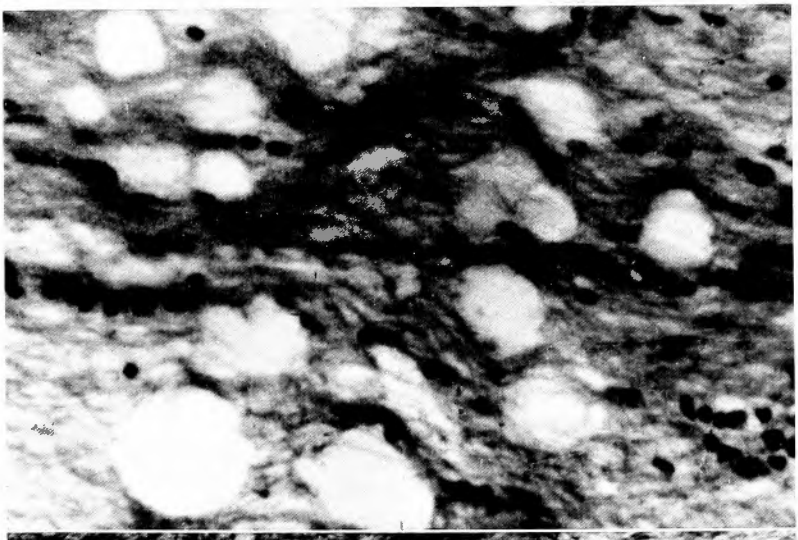

Fig. 19

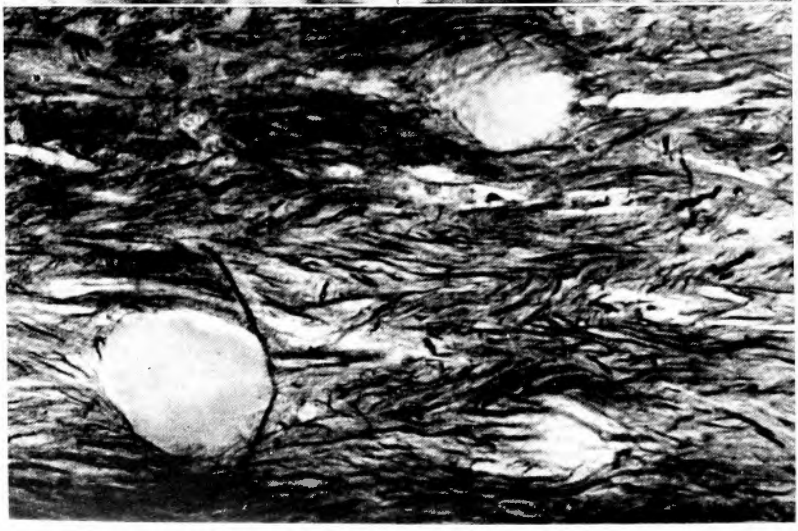

Fig. 20

EXPLANATION OF FIGURES

Figs. 1, 2 and 3. In dead fetuses, violent and extensive hemorrhages from rupture of superior cerebral veins, the sagittal sinus, the great vein of Galen and the cerebellar veins are observed.
Figs. 4, 5 and 6. Same cases. Hemorrhage into tela chorioidea.
Fig. 7. Case 4-1. Explosive hemorrhages from rupture of the superior cerebral veins.
Fig. 8. Same case. A large hematoma compressing the brain.
Fig. 9. Same case. Necrosis of the nerve cells.
Fig. 10. Case 5-1. Hemorrages from rupture of the superior cerebral veins, the great cerebral vein and the cerebellar veins.
Fig. 11. Same case. Necrosis of the frontal lobe.
Fig. 12. Same case. The other part of the brain remains intact.
Fig. 13. Case 5-2. Hemorrhages from rupture of the great cerebral vein and the superior cerebral veins.
Figs. 14 and 15. Same case. Hemorrhage from rupture of the great cerebral vein of Galen.
Fig. 16. Same case. Necrosis of the parietal lobe.
Fig. 17. Same case. The other part of the brain remains intact.
Figs. 18 and 19. Spongy degeneration throughout the brain.
Fig. 20. In areas of spongy degeneration, no axon is stained.

和 文 抄 録

酸素欠乏の家兎胎児脳及び成熟脳に及ぼす影響

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脳性小児麻痺の多くは出産時の障害に原因するものであつて，その主なる原因として分娩経過の異常によつておこる酸素欠乏のために頭蓋内出血が起ると云うことが注目されている．

著者は実験的にこの問題を検討するために，妊娠家兎を一定の容器内に収容して，徐々に酸素欠乏の状態をおこし，仮死状態を呈するに至つて，動物を容器外に取出し，人工呼吸によつて蘇生させた．酸素欠乏の持続時間は1時間半乃至3時間である．胎児は通常帝王切開により娩出させた．又成熟家兎にも同様の実験を行つた．

1) 妊娠家兎5例より14例の死産児と23例の生存児を得た．

2) 死産児の全例に上大脳静脈，矢状洞，大大脳静脈，上小脳静脈からの大量の出血が認められた．又脳組織も完全に壊死に陥つていた．

3) 生存児23例中11例にも同様の出血像が認められた．

4) 組織学的検索を行つた9例のうち，1例では広範な脳組織壊死が認められ，他の2例では夫々前頭葉及び頭頂葉の限局性壊死が認められた．

5) 成熟脳においては大脳，小脳の白質全般に脱髄像が認められた．

以上の実験成績から次の事が考えられる．即ち胎児の頭蓋内出血は酸素欠乏によつて起り得るものであつて，痙縮型の脳性麻痺のうち，Paraplegia は上大脳静脈よりの出血が大脳皮質運動領の下肢領域を障害した場合におこり，出血が更に皮質の下方に波及して上肢領域を障害すると Quadriplegia がおこり，重症の場合には除皮質の状態になり，Magnus and de Kleyn 緊張性頸反射や立直り反射が現われる様になると思われる．

又大大脳静脈の損傷がおこると，大脳核よりの血液の環流が障害されて，組織壊死を来し，高位除脳の状態を呈すると云うことが考えられる．